Estimates of the Number of U.S. Women Who Could Benefit From Tamoxifen for Breast Cancer Chemoprevention

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Background: **The Breast Cancer Prevention Trial demonstrated that tamoxifen treatment produced a 49% reduction in the risk of invasive breast cancer among women at elevated risk for the disease. The U.S. Food and Drug Administration (FDA) subsequently approved tamoxifen for women aged 35 years or older with a 5-year breast cancer risk of 1.67% or higher for breast cancer chemoprevention. However, tamoxifen use has been associated with adverse outcomes, and not all eligible women have a positive benefit/risk ratio.** ***Methods:*** **We used weighted data from the year 2000 National Health Interview Survey Cancer Control Module to estimate the total number of U.S. women, aged 35–79 years, who were eligible for tamoxifen chemoprevention based on the FDA eligibility criteria. We also estimated the numbers of white and black women who would benefit from tamoxifen chemoprevention on the basis of a positive benefit/risk index developed by Gail et al.** ***Results:*** **Of the 65 826 074 women aged 35–79 years without reported breast cancer in the United States in 2000, 10 232 816 women (15.5%, 95% confidence interval [CI] = 14.7% to 16.3%) would be eligible for tamoxifen chemoprevention. The percentage of U.S. women who would be eligible varied dramatically by race, with 18.7% (95% CI = 17.8% to 19.7%) of white women, 5.7% (95% CI = 4.3% to 7.5%) of black women, and 2.9% (95% CI = 2.1% to 3.9%) of Hispanic women being eligible. Of the 50 104 829 white U.S. women aged 35–79 years, 2 431 911 (4.9%, 95% CI = 4.3% to 5.4%) would have a positive benefit/risk index for tamoxifen chemoprevention. Of the 7 481 779 black U.S. women aged 35–79 years, only 42 768 (0.6%, 95% CI = 0.2% to 1.3%) would have a positive benefit/risk index. Among white women, 28 492 (95% CI = 24 693 to 32 292) breast cancers would be prevented or deferred if those women who have a positive net benefit index took tamoxifen over the next 5 years.** ***Conclusion:*** **A substantial percentage of U.S. women would be eligible for tamoxifen chemoprevention according to FDA criteria, but a much smaller percentage would have an estimated net benefit. Nevertheless, this latter percentage corresponds to more than two million women. [J Natl Cancer Inst 2003;95:526–32]**

Tamoxifen has usually been used by women diagnosed with advanced breast cancer to reduce their risk of recurrence and the development of a new tumor in the contralateral breast. Its ability to reduce the risk of contralateral breast cancer led investigators to examine the potential of tamoxifen to act as a chemopreventive agent in women at increased risk of breast cancer. The Breast Cancer Prevention Trial (BCPT) was a randomized, placebo-controlled study of the chemopreventive effects of tamoxifen in a population of women who had an elevated risk of breast cancer. Fisher et al. *(1)* published data from the BCPT that showed a 49% reduction in the risk of invasive breast cancer, a 50% reduction in the risk of noninvasive breast cancer, and marked reductions in the risk of fractures among the women who were assigned to receive tamoxifen during an average follow-up of 4 years. Unfortunately, some women in the BCPT also experienced adverse outcomes from tamoxifen use, including excesses of endometrial cancer, pulmonary embolism, stroke, deep vein thrombosis, and cataracts.

Several attempts have been made to understand the public health implications of the BCPT results. Fisher *(2)* estimated that, among the 29 million women in the United States who would have been eligible for the BCPT, 700 000 invasive and noninvasive breast cancers could have been prevented in 5 years. These estimates led him to conclude that "tamoxifen chemoprevention could potentially impart a substantial net benefit to the public health." Rockhill et al. *(3)* believed that these estimates were too high and misleading and came to a different conclusion: By applying the BCPT findings to the Nurses' Health Study population and using the U.S. Food and Drug Administration (FDA) eligibility criteria for tamoxifen chemoprevention (women at least 35 years of age with a 5-year risk of breast cancer of at least 1.67%), they concluded that far fewer breast cancers would be prevented by tamoxifen.

A full evaluation of the impact of tamoxifen chemoprevention on public health requires that both adverse events and proven benefits for breast cancer risk reduction be taken into account. An essential difficulty in doing so is the identification of women for whom the benefits outweigh the risks of adverse events. It is particularly important to identify subsets of women in which the tamoxifen-induced reductions in the absolute risks of breast cancer and other life-threatening or severe illnesses, such as hip fracture, exceed the increases in the absolute risk of serious or life-threatening tamoxifen-induced events, such as stroke, pulmonary embolism, or endometrial cancer.

To facilitate such identification, Gail et al. *(4)* created a tool for weighing the benefits and risks of tamoxifen. They combined information collected from the BCPT on the effects of tamoxifen with information from other sources on the background rates of various health outcomes in women who were not taking tamoxi-

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fen to estimate the effect of tamoxifen on the absolute risk of each outcome over 5 years for women aged 35–79 years. They proposed an overall benefit/risk index, which was computed as the net number of life-threatening events prevented (the total number of invasive breast cancers plus hip fractures minus the total number of endometrial cancers, strokes, and pulmonary embolisms) plus half the net number of serious events prevented (the number of *in situ* breast cancers minus the number of deep vein thromboses) over a 5-year period. This index corresponds to assigning a severity score of 0.5 for serious events and a severity score of 1.0 for life-threatening events. The benefit/risk index for a particular woman depended on age, race, risk factors for breast cancer, and whether a woman had a uterus. The benefit/risk index was tabulated for women with the 5-year risk of invasive breast cancer in the range of 1.5%–7.0%. Young women with high projected breast cancer risk typically had the most favorable benefit/risk indices. Gail et al. *(4)* identified subsets of women in which there was strong (probability $\geq$0.9) or moderate (probability $\geq$0.6) evidence that the benefit/risk index was greater than zero, indicating a net benefit.

Using this benefit/risk index, Rockhill et al. *(5)* examined the risks and benefits of tamoxifen use in a second analysis of the Nurses' Health Study dataset. They found that only a small proportion (3.3%) of women could be categorized as having strong evidence for a positive benefit/risk index.

Here we used nationally representative data from the year 2000 National Health Interview Survey (NHIS) to compare the number of U.S. women who would be eligible for tamoxifen chemoprevention, according to FDA eligibility criteria, with the number of women who have evidence of a positive benefit/risk index for breast cancer chemoprevention. To our knowledge, this is the first time that nationally representative estimates have been made of the number of women in the United States who are eligible for and would benefit from tamoxifen chemoprevention. These data can assist in evaluating the potential public health impact of tamoxifen use for breast cancer chemoprevention and may help identify subgroups of U.S. women who would especially benefit from chemopreventive efforts.

METHODS

Breast Cancer Risk Assessment

The year 2000 NHIS consisted of computer-assisted personal interviews of a nationally representative sample of 32 374 individuals. The NHIS is a continuous national interview survey of households in the United States and is a principal source of information on the health of the noninstitutionalized civilian population *(6).* The survey is conducted by the National Center for Health Statistics (Hyattsville, MD), administered by the U.S. Bureau of the Census, and is a publicly available resource *(6).* The NHIS uses a core questionnaire that provides national data on the incidence of illness and accidental injuries, the prevalence of chronic conditions and impairments, the extent of disability, and the use of health care services. The year 2000 NHIS contained an additional set of questions called the Cancer Control Module (CCM), which was designed and funded by the National Cancer Institute and the Centers for Disease Control and Prevention and covered cancer risk factors and screening practices. In each of the eligible 43 437 households selected to be interviewed with the core questionnaire, an adult respondent ($\geq$18 years old) was also asked to complete the CCM. The response rates for the eligible respondents to the NHIS core questionnaire and the CCM were 87.3% and 82.6%, respectively; the overall response rate was 72.1%.

The cancer screening section of the year 2000 NHIS CCM included questions that were part of a breast cancer predictive model developed by Gail et al. *(7).* This model calculates a woman's absolute risk of developing breast cancer over various time intervals, such as within the next 5 or the next 30 years *(7).* These questions collect information on age, age at first live birth, age at menarche, number of first-degree relatives with breast cancer, and number of breast biopsies. We used this model [as modified by Costantino et al. *(8)* and Anderson et al. *(9)* to project invasive cancer risk in the BCPT] to calculate the 5-year projected breast cancer risk for each of the 11 893 women who were between the ages of 35 and 79 years and completed the 2000 NHIS CCM. We excluded 355 of these women from further analysis because they reported having a diagnosis of breast cancer.

Tamoxifen Eligibility

The FDA eligibility criteria for tamoxifen chemoprevention—age 35 years or older and a 5-year risk of invasive breast cancer of at least 1.67%—is based on the model by Gail et al. *(7)* as modified by Costantino et al. *(8)* and Anderson et al. *(9).* We calculated the number of women, by race and age, who matched these criteria and would be eligible for tamoxifen chemoprevention by applying those 5-year projected breast cancer risk estimates to the 2000 NHIS CCM data. Our calculations of the total number of U.S. women who would be eligible for tamoxifen chemoprevention included white, black, and Hispanic women, as well as women who reported that they were of another race. Because of small numbers, estimates for women in the "other race" category are not presented separately in Table 1. Although the number of women of "other race" has only a small impact on the overall estimates for total U.S. women, they were included in the analysis for completeness.

Tamoxifen Benefit/Risk Index

We used data from the 2000 NHIS CCM to estimate the number of U.S. women who would potentially benefit from tamoxifen chemoprevention. Women were first categorized according to their 5-year projected breast cancer risk estimates, race, age, and whether they had a uterus. We then used the net benefit/risk indices presented in Tables 10 and 11 of Gail et al. *(4)* to calculate the number of white and black women, aged 35–79 years, in these categories who would have a positive benefit/risk index (probability $\geq$0.6). Although the FDA eligibility criteria for tamoxifen chemoprevention include a 5-year risk of invasive breast cancer of at least 1.67%, we calculated the number of women with a positive net benefit/risk index, even for women with a 5-year risk of invasive breast cancer, of at least 1.50% as presented in Tables 10 and 11 of Gail et al. *(4).* We used this lower risk cutoff to include most women aged 35 years or older who could potentially benefit from tamoxifen, even though some would not fulfill FDA eligibility requirements. Using the breast cancer predictive model by Gail et al. *(7)* as modified by Costantino et al. *(8)* and Anderson et al. *(9),* we also estimated the number of breast cancers that would be prevented or deferred over the next 5 years among white women who would benefit from tamoxifen, assuming a 49% risk reduction for breast cancer for tamoxifen as reported by Fisher et al. *(1).*

Table 1. Estimates of the total number of U.S. women eligible for tamoxifen chemoprevention according to FDA eligibility criteria, by race and age groups, using weighted data from the year 2000 NHIS CCM*

	All women†			White women			Black women			Hispanic women		
Age group, y	Total No. (NHIS sample size)	No. eligible for tamoxifen (NHIS sample size)	Percentage eligible for tamoxifen (95% CI)	Total No. (NHIS sample size)	No. eligible for tamoxifen (NHIS sample size)	Percentage eligible for tamoxifen (95% CI)	Total No. (NHIS sample size)	No. eligible for tamoxifen (NHIS sample size)	Percentage eligible for tamoxifen (95% CI)	Total No. (NHIS sample size)	No. eligible for tamoxifen (NHIS sample size)	Percentage eligible for tamoxifen (95% CI)
35–79	65 826 074 (11 538)	10 232 816 (1769)	15.5 (14.7 to 16.3)	50 104 829 (7728)	9 377 715 (1582)	18.7 (17.8 to 19.7)	7 481 779 (1804)	430 057 (99)	5.7 (4.3 to 7.5)	5 813 012 (1645)	167 485 (50)	2.9 (2.1 to 3.9)
35–39	11 384 220 (1979)	8309 (2)	0.1 (0.0 to 0.3)	7 906 861 (1159)	0 (0)	0.0 (0.0 to 0.3)	1 522 332 (357)	8309 (2)	0.5 (0.1 to 2.0)	1 309 812 (366)	0 (0)	0.0 (0.0 to 1.0)
40–49	21 092 915 (3487)	960 883 (142)	4.6 (3.7 to 5.4)	15 577 412 (2199)	831 199 (119)	5.3 (4.2 to 6.4)	2 559 253 (596)	64 601 (12)	2.5 (1.1 to 5.0)	2 081 708 (568)	13 554 (5)	0.7 (0.1 to 1.9)
50–59	14 994 216 (2542)	1 979 185 (302)	13.2 (11.6 to 14.8)	11 699 803 (1754)	1 803 782 (262)	15.4 (13.5 to 17.3)	1 715 650 (408)	123 405 (28)	7.2 (4.1 to 11.6)	1 092 643 (305)	18 659 (7)	1.7 (0.6 to 3.9)
60–69	9 988 403 (1819)	3 292 131 (553)	33.0 (30.5 to 35.4)	7 979 454 (1299)	3 008 966 (490)	37.7 (34.9 to 40.6)	915 010 (245)	104 508 (26)	11.4 (6.6 to 18.1)	823 861 (235)	80 832 (21)	9.8 (5.5 to 15.8)
70–79	8 366 320 (1711)	3 992 308 (770)	47.7 (44.7 to 50.7)	6 941 299 (1317)	3 733 768 (711)	53.8 (50.5 to 57.0)	769 534 (198)	129 234 (31)	16.8 (9.8 to 26.0)	504 988 (171)	54 440 (17)	10.8 (5.3 to 19.0)

*Five-year projected risk of invasive breast cancer is greater than or equal to 1.67%. FDA = U.S. Food and Drug Administration; NHIS = National Health Interview Survey; CCM = Cancer Control Module; CI = confidence interval.

†Estimates for all women include white women, black women, Hispanic women, and women of other races.

Benefit/risk indices for tamoxifen have not been developed for Hispanic women, and therefore estimates of the numbers of Hispanic women who would benefit from tamoxifen use could not be calculated.

We also conducted several sensitivity analyses with respect to the benefit/risk index. We examined the effect of changing the criterion for a positive benefit/risk index from moderate evidence (probability ≥ 0.6) to strong evidence (probability ≥ 0.9) on the percentage of white women who would benefit from tamoxifen. We also determined the percentage of white women who would benefit from tamoxifen if we relaxed our criterion to include all women whose positive benefit/risk index exceeded zero, regardless of the probability that exceeding zero was due to chance. We examined the effect of changing the value of the severity score of various clinical outcomes used in the net benefit/risk indices on the percentage of women that would benefit from tamoxifen. In our sensitivity analyses, we changed the severity score in the original benefit/risk index from 0.5 (severe event) to 0 (other events) for *in situ* breast cancer. We also examined the effect of changing the severity score for endometrial cancer from 1 (life-threatening event) in the original benefit/risk index to 0.5 (severe event).

All estimates, including totals and percentages, were weighted by the NHIS sample weights to the total U.S. population, and standard errors used in computing the 95% confidence intervals (CIs) were estimated to take into account the complex multistage probability sampling design of the NHIS *(10).* The NHIS sample weights are a product of four factors: 1) the inverse of the probability of selection (e.g., households with black and/or Hispanic residents were sampled with higher probabilities than were households with white residents); 2) an adjustment for sampled households that did not respond to the interview; 3) an adjustment, called a first-stage ratio adjustment, that stabilized the contribution of the smaller sampled areas of the United States to the estimation; and 4) a post-stratification adjustment that ensured that NHIS estimates of the U.S. population sizes for predetermined demographic categories agreed with U.S. Bureau of the Census population sizes. For the estimates presented in this article, the sample observations were inflated by the sample weights to reflect their representation in the U.S. population, resulting in approximately unbiased estimates. We took into account the weighting and the stratified hierarchical cluster sampling of the NHIS in estimating the standard errors by using Taylor linearization *(11)* and approximating the NHIS sample design as a selection of two primary sample units (first sampling units) from 187 strata with replacement. This method is described in an unpublished National Center for Health Statistics document found at http://www.cdc.gov/nchs/data/nhis/pvar.pdf. We calculated CIs for small percentages, for which the numerators were computed from sample sizes greater than zero but less than 100, by using a modified binomial CI *(11).* This modification expands the classical binomial CI by a factor that reflects the increase in variance of the estimated percentage due to the weighting and complex sampling. CIs for zero percentages were computed by using the classical binomial CI method, and all other CIs for percentages were calculated by using normal approximation *(11).* In an age-by-race cell, we computed CIs for the total numbers of women eligible for tamoxifen by multiplying the estimated total number of women in that cell by the limits of the CI for the estimated percentage of women eligible for tamoxifen in that same cell. All calculations were performed using SAS version 8.2 and SAS callable SUDAAN version 8.0 software *(12,13).*

Results

Table 1 shows estimates of the total number of U.S. women, by race and age groups, eligible for tamoxifen chemoprevention according to FDA eligibility criteria. For all 65 826 074 women aged 35–79 years in the U.S. population, 10 232 816 (15.5%, 95% CI = 14.7% to 16.3%) women would be eligible for tamoxifen chemoprevention on the basis of their age and breast cancer risk factors. The percentage of eligible women for tamoxifen chemoprevention increases with increasing age. Only 0.1% of

women aged 35–39 years would be eligible, whereas 4.6% of women aged 40–49 years, 13.2% of women aged 50–59 years, 33.0% of women aged 60–69 years, and 47.7% of women aged 70–79 years would be eligible. The percentage of U.S. women who would be eligible for tamoxifen chemoprevention varies dramatically by race, with 18.7% of white women, 5.7% of black women, and 2.9% of Hispanic women being eligible.

Table 2 shows weighted estimates of the total number of white and black U.S. women, both with and without a uterus, who would benefit from tamoxifen chemoprevention based on evidence for a positive benefit/risk index (probability ⩾0.6) as calculated with the use of the benefit/risk indices presented in Tables 10 and 11 of Gail et al. *(4).* Of the 50 104 829 white women aged 35–79 years, we found that 2 431 911 (4.9%, 95% CI = 4.3% to 5.4%) would benefit from tamoxifen chemoprevention. The percentage of white women who would benefit varies by age, with 0% of women aged 35–39 years benefiting, 8.1% of women aged 40–49 years benefiting, 8.5% of women aged 50–59 years benefiting, 2.1% of women aged 60–69 benefiting, and 0.1% of women aged 70–79 years benefiting. Absence of a uterus was an important factor in determining benefit. Overall, 59.4% (95% CI = 53.4% to 65.4%) of the white women who would benefit from tamoxifen reported having had a hysterectomy (data not shown). Among those who would benefit, the percentage who had had a hysterectomy varied by age: 24.7% (95% CI = 16.9% to 33.9%) of women aged 40–49 years, 96.5% (95% CI = 93.7% to 99.3%) of women aged 50–59 years, and 100% (95% CI = 86.8% to 100%) of women aged 60–79 reported having had a hysterectomy (data not shown).

When we used a more stringent criterion to define categories of women who would benefit, the percentage of women in each category decreased (data not shown). For example, if we required that there be strong evidence (probability ⩾0.9) that the benefit/risk index for tamoxifen be positive, the percentage of white women estimated to benefit decreased from 4.9% (95% CI = 4.3% to 5.4%) to 2.9% (95% CI = 2.4% to 3.3%). This difference is due largely to a decrease in the percentage of women in the 50–59 year age group who would benefit, which was 8.5% (95% CI = 7.2% to 9.8%) for a probability of at least 0.6 and only 0.9% (95% CI = 0.4% to 1.5%) for a probability of at least 0.9. When we relaxed our criterion to include all white women whose benefit/risk index exceeded 0, the percentage of women benefiting increased only slightly, to 5.7% (95% CI = 5.2% to 6.3%) (data not shown).

Changing the assumptions made for the severity scores associated with various clinical outcomes used in the net benefit/risk indices also influenced our estimates of the number of women who would benefit from tamoxifen (data not shown). When we changed the severity score of 0.5 (severe event) to 0 (other events) for *in situ* breast cancer in the original benefit/risk index, the percentage of white women estimated to benefit was reduced from 4.9% (95% CI = 4.3% to 5.4%) to 3.8% (95% CI = 3.3% to 4.3%), for a positive probability of at least 0.6 for the benefit/risk index. When we changed the severity score for endometrial cancer from 1 (life-threatening event) to 0.5 (severe event), the percentage of white women estimated to benefit increased only slightly, from 4.9% (95% CI = 4.3% to 5.4%) to 5.2% (95% CI = 4.6% to 5.7%), for a probability of at least 0.6.

We estimate that, among the white women who would benefit from tamoxifen, 58 148 invasive breast cancers (95% CI = 50 394 to 65 903 cancers) will develop over the next 5 years. If all 2 431 911 white women who stand to benefit take tamoxifen over the next 5 years, and if the risk reduction of 49% reported by Fisher et al. *(1)* applies, then 28 492 of these breast cancers (95% CI = 24 693 to 32 292 cancers) could be prevented or deferred.

We estimate that, of the 7 481 779 black U.S. women between the ages of 35 and 79 years, only 42 768 (0.6%, 95% CI = 0.2% to 1.3%) would benefit from tamoxifen chemoprevention. The number of black women who reported having had a hysterectomy was too small to provide reliable estimates of those who would benefit from tamoxifen. Estimates for Hispanic U.S. women and women of other races could not be calculated because benefit/risk indices for these races have yet to be developed *(4).*

Discussion

The BCPT demonstrated a striking 49% reduction in the risk of invasive breast cancer among women who took the chemopreventive agent tamoxifen for 5 years. This finding has prompted many investigators to attempt to describe the public health impact on breast cancer prevention in the United States if tamoxifen were prescribed for women at high risk of breast cancer. As was recently demonstrated for hormone replacement therapy *(14),* however, evaluating the true public health impact of U.S. women taking tamoxifen requires weighing the benefits of reducing invasive breast cancer and bone fractures against the adverse effects of increased risks of endometrial cancer, pulmo-

Table 2. Estimates of the total number of white and black U.S. women who would benefit from tamoxifen chemoprevention, by age, using weighted data from the year 2000 NHIS CCM*

	White women			Black women		
Age group, y	Total No. (NHIS sample size)	No. benefiting from tamoxifen (NHIS sample size)	Percentage benefiting from tamoxifen (95% CI)	Total No. (NHIS sample size)	No. benefiting from tamoxifen (NHIS sample size)	Percentage benefiting from tamoxifen (95% CI)
35–79	50 104 829 (7728)	2 431 911 (353)	4.9 (4.3 to 5.4)	7 481 779 (1804)	42 768 (7)	0.6 (0.2 to 1.3)
35–39	7 906 861 (1159)	0 (0)	0.0 (0.0 to 0.3)	1 522 332 (357)	10 413 (3)	0.7 (0.1 to 2.1)
40–49	15 577 412 (2199)	1 263 824 (175)	8.1 (6.8 to 9.4)	2 559 253 (596)	32 355 (4)	1.3 (0.3 to 3.7)
50–59	11 699 803 (1754)	996 231 (152)	8.5 (7.2 to 9.8)	1 715 650 (408)	0 (0)	0.0 (0.0 to 0.9)
60–69	7 979 454 (1299)	163 667 (24)	2.1 (1.3 to 3.0)	915 010 (245)	0 (0)	0.0 (0.0 to 1.5)
70–79	6 941 299 (1317)	8189 (2)	0.1 (0.0 to 0.4)	769 534 (198)	0 (0)	0.0 (0.0 to 1.8)

*Moderate evidence (probability ⩾0.6) that the benefit/risk index exceeded zero indicating a net benefit, taking random variation into account *(4).* NHIS = National Health Interview Survey; CCM = Cancer Control Module; CI = confidence interval.

nary embolism, stroke, and deep vein thrombosis. In this article, we used nationally representative data to compare the number of women in the United States who would be eligible for tamoxifen according to FDA eligibility criteria with the number of women who, based on benefit/risk indices developed by Gail et al. *(4),* would benefit from tamoxifen chemoprevention.

Soon after results from the BCPT about the chemopreventive effects of tamoxifen were published, the FDA issued eligibility criteria for tamoxifen chemoprevention, namely, being at least 35 years old and having a 5-year risk of invasive breast cancer of at least 1.67%. This projected risk of invasive breast cancer, which was based on a modification *(8,9)* of a model developed by Gail et al. *(7)* that used a woman's age and breast cancer risk factors, was used as an eligibility criterion for the BCPT. Using data from the 2000 NHIS CCM, we estimate that 15.5% (N = 10 232 816) of women aged 35–79 years in the United States would be eligible for tamoxifen chemoprevention on the basis of their age and breast cancer risk factors. Because breast cancer incidence rates increase with increasing age, it is not surprising that the percentage of women eligible for tamoxifen chemoprevention increases dramatically with age, with 45% of white women older than 60 years of age being eligible. A higher percentage of women eligible for tamoxifen were white (18.7%) than were black (5.7%) or Hispanic (2.9%). These large differences are likely the result of 1) the low prevalence of breast cancer risk factors among blacks and Hispanics and 2) the lower baseline incidence rates for breast cancer for blacks and Hispanics (compared with those for whites) used in the Gail breast cancer predictive model. Some evidence exists that the baseline incidence rates for breast cancer may be underestimated for black women younger than 50 years *(4,15).* Our data may explain, in part, the difficulty of identifying and recruiting minority women at high risk of breast cancer for trials of breast cancer chemopreventive agents—that is, few of them have an estimated risk of invasive breast cancer high enough to make them eligible to participate in such a trial.

Although a substantial percentage of U.S. women would be eligible for tamoxifen according to FDA eligibility criteria, a much smaller percentage would actually benefit from tamoxifen use. In this study, we weighed life-threatening and severe outcomes, as described in Gail et al. *(4),* to determine whether a woman would have a net benefit from tamoxifen chemoprevention, and we counted only those categories of women in which there was at least moderate evidence (probability $\geq$0.6) that the net benefit exceeded zero. Using this criterion, we estimate that only 4.9% of white U.S. women would benefit from tamoxifen. Although this percentage is much smaller than the percentage of white women eligible for tamoxifen (18.7%), it nonetheless corresponds to a substantial number of women (N = 2 431 911). These data also indicate that, whereas the percentage of women eligible for tamoxifen is highest among women in the 60–79 year age group, the proportions of white women who will benefit are greatest in the 40–49 year and 50–59 year age groups, in which 8.1% and 8.5% would benefit, respectively. This pattern reflects the high proportion of women aged 40–59 years in the current U.S. population and the fact that the benefit/risk index decreases with increasing age as adverse side effects associated with tamoxifen use become more common. It is interesting to note that, among women aged 50 years or older, with few exceptions, only those with a hysterectomy had a positive benefit/risk index. Having a hysterectomy eliminates the risk of endometrial cancer; thus, our data demonstrate the important role that endometrial cancer plays in the benefit/risk index for women aged 50 years or older.

Although FDA eligibility criteria specify that a 5-year invasive breast cancer risk of 1.67% is necessary for tamoxifen chemoprevention eligibility, our data, which are based on benefit/risk indices, demonstrate that a substantial number of white women with a risk less than 1.67% but greater than 1.5% would also benefit from tamoxifen use. For example, among white women in the 40–49 year age group, only 5.3% would be eligible for tamoxifen according to FDA eligibility criteria, but 8.1% would benefit on the basis of the benefit/risk index. This difference reflects the substantial number of women in this age group who have a 5-year invasive breast cancer risk greater than 1.5% but less than the 1.67% defined by FDA eligibility criteria. By contrast, most of the older women with a risk greater than 1.67% would not benefit from tamoxifen because of the high incidence of adverse side effects from tamoxifen in older women.

Although approximately 6% of black women would be eligible for tamoxifen, our analysis suggests that a very small percentage (0.6%) would derive any net benefit from its use. Proportionally fewer black women than white women in the United States have an estimated net benefit from taking tamoxifen, because the estimated risk of breast cancer among black women in the general population is relatively low and because the estimated baseline rates of stroke, pulmonary embolism, and deep vein thrombosis are higher among black women than among white women *(4).* Estimates of the number of Hispanic women who would benefit from tamoxifen use could not be calculated because benefit/risk indices for tamoxifen have not been developed for Hispanic women.

Our estimates are surprisingly insensitive to the choice of severity scores assigned to various clinical outcomes and the criterion defining a positive benefit/risk index, namely, any positive value or a positive value with probability exceeding 0.6 or 0.9. Sensitivity analyses also confirm that the number of women likely to have a net benefit from using tamoxifen, on the basis of the benefit/risk indices presented in Gail et al. *(4),* is considerably smaller than the number of women who are eligible to use tamoxifen according to FDA eligibility criteria. Our findings are further supported by the analysis of Rockhill et al. *(5),* who reported that only 3.3% of their Nurses' Health Study population showed strong evidence (probability $\geq$0.9) of a positive benefit/risk index.

The benefit/risk index developed by Gail et al. *(4)* uses only the results from the BCPT, which showed a protective relative risk of 0.51 for invasive breast cancer associated with tamoxifen use. However, two European trials *(16,17)* of tamoxifen and breast cancer risk failed to demonstrate a statistically significant protective effect for tamoxifen chemoprevention. By combining all the available data, Gail et al. *(4)* calculated a protective relative risk of 0.59 for tamoxifen. This attenuation of the effects of tamoxifen reduces the estimates of the number of women who would benefit from tamoxifen chemoprevention. The International Breast Cancer Prevention Study *(18)* recently reported a protective relative risk for breast cancer of only 0.68 (95% CI = 0.50 to 0.92).

Of the 9 377 715 white U.S. women who would be eligible for tamoxifen chemoprevention, we estimate that less than one-third (N = 2 431 911) would derive a net benefit from taking the drug on the basis of their age and breast cancer risk factors. We

estimate that, among the white women who would benefit from tamoxifen, approximately 58 148 invasive breast cancers will develop over the next 5 years. If all 2 431 911 women with an estimated net benefit/risk index took tamoxifen over the next 5 years, and if the risk reduction of 49% reported by Fisher et al. *(1)* applies, then 28 492 of these breast cancers would be prevented, or deferred, which would be a substantial achievement. Fisher's *(2)* estimate that 700 000 invasive cancers could be prevented with tamoxifen assumed that all women eligible for the BCPT would be treated, not just those for whom treatment affords a net benefit.

The breast cancer risk model used in these analyses *(7)* has only limited ability to discriminate between women who will develop breast cancer and women who will not *(3),* even though the model provides good estimates of the probability that a woman will develop breast cancer *(3,8).* Calibration of the model to predict these probabilities can be assessed by comparing the observed number of breast cancers with the expected number in various subgroups of women. Some might argue that one should not recommend a course of medical management, such as taking or not taking tamoxifen, unless one is able to foretell the individual's outcome with precision. Most clinicians weigh the risks and benefits associated with a particular treatment, however, and recommend the course of action that has the most favorable expected net effect. For example, a doctor might recommend an antihypertensive medication for a person with only moderately elevated blood pressure, even though a moderate elevation in blood pressure cannot reliably discriminate between a person who will die from cardiovascular disease in the next 5 years and one who will not. Moreover, the clinical trials that provide evidence of a benefit of treatments such as antihypertensive agents rely on comparisons of groups of individuals. However much one would like to have a treatment tailored to an individual, the best available evidence to guide treatment decisions is based on the resemblance of an individual to a group.

Not everyone would agree with the criteria used by Gail et al. *(4)* to determine a net benefit/risk index, particularly as it pertains to counseling an individual woman on the appropriate therapy for her situation. Although a benefit/risk index is useful for making population estimates, it may not appropriately measure the net benefit for a particular woman because it does not include all health risk and protective factors for the disease. For example, women who exercise regularly may have lower risk of cardiovascular disease than women of the same age and ethnic group in the general population, which could mitigate adverse outcome factors in the benefit/risk index. Such women, therefore, would have a more favorable benefit/risk index than we used in our calculations [see Table 12 in *(4)*]. Therefore, the benefit/risk index should not be the sole basis for decision making regarding the use of tamoxifen for breast cancer risk reduction therapy. Counseling individual women about tamoxifen chemoprevention must involve both fully informing a woman of her disease risk and benefits and considering her comorbidities, personal values, preferences, lifestyle, and specific medical situation. These issues are especially important when counseling minority women about tamoxifen chemoprevention, because limited predictive information for their health risk profiles is available.

Our results for black women are less stable than those for white women, not only because of the higher uncertainty in projecting breast cancer risk among black women, but also because the estimated beneficial and adverse effects of tamoxifen from the BCPT primarily reflect the outcomes in white women, who comprised 96.5% of the study population. Because incidence rates for stroke, pulmonary embolism, and deep vein thrombosis are not available for black women, Gail et al. *(4)* extrapolated data from mortality databases to develop the benefit/risk indices for black women *(19).* The validity of the assumptions used for extrapolation and the accuracy of these rates have not been determined. For these reasons, the estimates we present in Table 2 may not give a complete picture of the numbers of black women who might benefit from tamoxifen.

The precision of breast cancer risk prediction models and benefit/risk indices for tamoxifen chemoprevention is highly dependent on the availability and quality of health outcomes data, not only those for breast cancer, but also for other outcomes, such as stroke. Efforts to collect more accurate data on various health outcomes and in various populations are needed to improve our prediction models and our assessments of the risks and benefits of health outcomes associated with tamoxifen chemoprevention.

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NOTES

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